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(71) Applicant *(for all designated States except US)*: ALCON, INC. [CH/CH]; P.O. Box 62, Bosch 69, CH-6331 Hunenberg (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: YANNI, John, M. [US/US]; 2821 Donnybrook Drive, Burleson, TX 76028 (US). GAMACHE, Daniel, A. [US/US]; 5610 Hunterwood Lane, Arlington, TX 76017 (US). MILLER, Steven T. [US/US]; 5902 Canberra Lane, Arlington, TX 76017 (US).

(74) Agents: YEAGER, Sally, S. et al.; R & D Counsel, Mail Code Q-148, 6201 South Freeway, Fort Worth, TX 76134 (US).

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WO 03/049770 A1

(54) Title: USE OF AN H_1 ANTAGONIST AND A SAFE STEROID TO TREAT RHINITIS

(57) Abstract: Compositions and methods for treating rhinitis with H_1 antagonists/antiallergics and safe steroids are disclosed.

USE OF AN H_1 ANTAGONIST AND A SAFE STEROID TO TREAT RHINITIS

The present invention is directed to the use of an H_1 antagonist/antiallergic in combination with a safe steroid to treat nasal conditions, specifically rhinitis.

Background of the Invention

Allergic rhinitis has historically been treated with a regimen of oral antihistamines and/or oral steroids. Systemic treatment typically requires higher concentrations of the drug compound to be administered to afford an effective concentration to reach the necessary treatment site. Antihistamine compounds are known to have central nervous system (CNS) activity which manifests itself in drowsiness. They may also have anticholinergic activity which manifests itself in the drying of mucus membranes. Steroid therapy whether dosed orally or intranasally can also produce significant systemic side effects, including adrenal insufficiency, cardio-vascular irregularities, and immunosuppression. Growth retardation is an especially important concern in allergic pediatric patients.

Intranasal combination therapy is known. For example, WO 97/01337 discloses combinations of topical nasal antihistamines and topical nasal steroids for the treatment of rhinitis. It does not disclose the use of the safe steroids of the present invention. WO 97/46243 discloses a nasal spray containing a steroid and an antihistamine. This publication does not disclose or suggest the use of a safe steroid. There are also intranasal products containing both a steroid and an antihistamine, among other active ingredients, (e.g., Cortinasal from Pharmacobel; Neovvine from Dupa; Nicorin from Rontag; Rinosular from SmithKline Beecham; Rinocusi from Cusi; and Comfonin from Meider.)

The use of an H_1 antagonist/antiallergic in combination with a safe steroid for treating rhinitis is not known.

Summary of the Invention

The present invention is directed to intranasal compositions of combinations of H_1 antagonists/antiallergic and safe steroids to treat rhinitis. Methods for the use of the compositions in mammals are also contemplated.

Description of Preferred Embodiments

The current invention comprises compositions of H_1 antagonists/antiallergics for treating the sneezing and rhinorrhea associated with allergic rhinitis. The compositions also include a safe steroid, as used herein the term "safe steroid" means a steroid which treats eosinophil and neurotrophil associated inflammation with resultant congestion but has either a lack of systemic bioavailability or is rapidly deactivated after systemic absorption.

The H_1 antagonists/antiallergics which are useful according to the present invention include all efficacious compounds, including, but not limited to: emedastine, loratadine, 5-[2-[4-bis(4-fluorophenyl)hydroxymethyl-1-piperidinyl]ethyl]-3-methyl]-2-oxazolidinone ethanedioate), desloratadine, azelastine, olopatadine, levocabastine, epinastine, and ketotifen.

Safe steroids which can be used herein include any glucocorticoid which meets the safe steroid definition, including but not limited to, rimexolone and loteprednol.

The H_1 antagonists/antiallergics and safe steroids (compounds) can be incorporated into various types of intranasal formulations for delivery to the nose. For example, intranasal formulations may contain preservatives, such as, benzalkonium chloride, EDTA, and tromethamine; viscosity modifiers, such as, hydroxy propyl methyl cellulose (HPMC) and related agents; toxicity adjusting agents, for example, sodium chloride (NaCl); wetting agents/surfactants, such as, tyloxapol or Polysorbate 80; pH adjusters; and water.

The compounds are preferably formulated as intranasal suspensions or solutions, with a pH of about 6.0 to 8.0. The H_1 antagonists/antiallergics will normally be contained in these formulations in an amount 0.01% to 0.5%

by weight, but preferably in an amount of 0.02% to 0.1% by weight. The safe steroids will normally be contained in those formulations in an amount 0.05% to 1.5% by weight, but preferably in an amount of 0.1% to 1.0% by weight. Thus, for intranasal presentation 1 to 2 sprays of these formulations would be delivered to the nostrils up to 2 times per day according to the routine discretion of a skilled clinician

The preferred compositions of the present invention includes olopatadine (0.1%) with rimexolone (0.1%) and emedastine 0.05% with rimexolone (0.1%).

The following example is illustrative of a composition of the present invention, but is in no way limiting.

EXAMPLE

Ingredient	Weight %
Emedastine	0.05%
Rimexolone	0.1%
Benzalkonium chloride	0.01%
Tromethamine	0.5%
Disodium EDTA	0.01%
Sodium Chloride (Adjust isotonicity to 280mOsmols/kg)	0.6 to 0.8%
HPMC	0.1 to 0.5%
Tyloxapol	0.05%
NaOH and/or HCl	QS to pH 7.4
Purified water	QS to 100%

We Claim:

1. A method of treating rhinitis in mammals which comprises administering a pharmaceutically effective amount of a composition comprising an H_1 antagonist/antiallergic and a safe steroid.

2. The method of Claim 1 wherein the composition comprises an H_1 antagonist/antiallergic selected from the group consisting of emedastine, loratadine, 5-[2-[4-bis(4-fluorophenyl)hydroxymethyl-1-piperidinyl]ethyl]-3-methyl]-2-oxazolidinone ethanedioate), desloratadine, azelastine, olopatadine, levocabastine, epinastine, and ketotifen.

3. The method of Claim 1 wherein the composition comprises a safe steroid selected from the group consisting of rimexolone and loteprednol.

4. The method of Claim 2 wherein the composition comprises an antagonist/antiallergic selected from the group consisting of emedastine, olopatadine, and desloratadine.

5. A method of treating rhinitis in mammals which comprises administering a pharmaceutically effective amount of a composition comprising emedastine and rimexolone.

6. A method of treating rhinitis in mammals which comprises administering a pharmaceutically effective amount of a composition comprising olopatadine and rimexolone.

7. A method of treating rhinitis in mammals which comprises administering a pharmaceutically effective amount of a composition comprising desloratadine and rimexolone.

INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/US 02/36915

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K31/575 A61K31/551 A61K31/335 A61K31/451
A61P11/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 199 47 234 A (ASTA MEDICA AG) 5 April 2001 (2001-04-05) page 2, line 47 -page 3, line 6 tables 1,2 claims 1-5,12	1-3
A	WO 01 35963 A (ALCON UNIVERSAL LTD ;YANNI JOHN M (US)) 25 May 2001 (2001-05-25) page 2, line 20 -page 4, line 7	1,2
A	WO 97 01337 A (MCNEIL PPC INC) 16 January 1997 (1997-01-16) cited in the application page 1, line 9 - line 26	1-7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 April 2003	16/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paul Soto, R

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HOCHHAUS G ET AL: "BINDING AFFINITIES OF RIMEXOLONE ORG-6216 FLUNISOLIDE AND THEIR PUTATIVE METABOLITES FOR THE GLUCOCORTICOID RECEPTOR OF HUMAN SYNOVIAL TISSUE" AGENTS AND ACTIONS, vol. 30, no. 3-4, 1990, pages 377-380, XP009008536 ISSN: 0065-4299 the whole document	1-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/36915

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-7 (industrial applicability)
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1-4 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

Continuation of Box I.1

Claims Nos.: 1-7 (industrial applicability)

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Claims Nos.: 1-4 (in part)

Present claims 1-4 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, both with respect to the H1 antagonist/antiallergic and the safe steroid, that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Furthermore, the definition of the second component is also unclear (Art. 6 PCT) because of the term "safe". This term is vague, has no well-recognised meaning in the art, and leaves the reader in doubt about the steroids falling within the scope of said definition.

As a result, the lack of clarity is such so as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and consice); namely in respect of the specific H1 antagonists/antiallergic mentioned in claims 2 and 4, and the steroids mentioned in claim 3, rimexolone and loteprednol.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/US 02/36915

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19947234 A	05-04-2001	DE 19947234 A1	05-04-2001
		AU 7907300 A	30-04-2001
		BR 0014312 A	21-05-2002
		CZ 20021014 A3	12-06-2002
		WO 0122955 A2	05-04-2001
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		BR 0015647 A	16-07-2002
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